REMARKS

The Office Action has been carefully reviewed. No claim is allowed. Claims 3 and 17-20 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

The Information Disclosure Statement filed January 10, 2002, has been acknowledged but the references have not been considered because they seem to have been misplaced by the USPTO. The examiner requests applicants' help in obtaining copies of all references listed on the PTO-1449.

Attached hereto for the examiner's convenience are copies of the references listed on PTO-1449 form filed with the application on January 10, 2000.

The disclosure has been objected to because text is considered to be missing in line 25 on page 13 and line 2 on page 27.

What is missing is a period at the end of the sentence. Appropriate correction is made to the specification, thereby obviating this objection.

Claims 3, 9, 12, 15, and 17 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite and as being incomplete for omitting essential steps.

The amendments to the claims obviate the 112, second paragraph, rejections.

Claims 3, 9, 12, 15, and 17 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is respectfully traversed.

In order to make and/or use the claimed invention, the following would be necessary:

(i) tumor cells collected from a patient (cells to be transformed);

(ii) a composition comprising an isolated DNA molecule that comprises a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:1 (genomic DNA or a fragment thereof);

(iii) a method for transforming the cells of (i)

(iv) a method for proliferating in vitro the transformant obtained in (iii); and

(v) a method for transplanting the proliferated transformed cells of (iv) into a patient.

All of the above, however, are believed to be easily available or easily capable of being conducted by one of skill in the art based on the disclosure of the present specification and/or state of the art at the time the invention was made. First, it is clear that tumor cells as recited in (i) are easily available to one skilled in the art. Furthermore, the methods as recited in (iii) to (v) *per se*

were already well known to one skilled in the art at the time the claimed invention was made. Finally, with respect to a composition as recited in (ii), while it would have been difficult to obtain the composition without the disclosure of the present specification, it is believed that the specification provides sufficient and detailed disclosure for one of skill in the art to obtain such a composition without undue experimentation.

Furthermore, the specification from page 11, line 3 to page 12, line 12 provides sufficient guidelines which are considered to be necessary for one of skill in the art to understand and reduce to practice a method for treating tumors using gene therapy as recited in claim 3. That is to say, the specification discloses, citing, for example, "Jikken-Igaku-Bessatsu-Biomanual UP Series Idenshichiryo-no-Kisogijutsu (Basic techniques for the gene therapy)" (1996), general procedures for gene therapy which are applicable to the present invention. Furthermore, as evident from the copies of U.S. Patents 5,399,346 and 5,478,745, attached hereto, the technique of gene therapy has been well known one of skill in the art at the time the present invention was made.

It should be easy for one of skill in the art to transplant genomic DNA of the present invention as recited in (ii) into a patient according to the well known technique of gene therapy. For example, one of skill in the art can transplant the genomic DNA into tumor cells recited in (i)

using conventional virus, such as retrovirus, adenovirus and adeno-associated virus, as vector. Alternatively, one of skill in the art may transplant the genomic DNA into a patient by incorporating the genomic DNA into cationic- or membrane fusible-liposomes, or by self-transplanting lymphocytes which are collected from the patient before the DNA is introduced. See page 11 of the specification.

Genomic DNA can be applicable to adoptive immunotherapy and tumor vaccine therapy as set forth on page 11, lines 12-20 of the specification. Genomic DNA of the presently claimed invention exhibits considerable effect in gene therapy for diseases including viral diseases, microbial diseases, malignant tumors and immunopathies as described on page 11, lines 23-25. These effects are reasonably understood from the fact that IL-18 is capable of inducing the production of IFN-γ and as well as of enhancing killer cells' cytotoxicity, and is thus effective as an anti-tumor agent. Japanese Patent Application No. 28,722/96, cited at page 11, lines 2-3 of the specification discloses the usefulness of IL-18 as an anti-tumor agent, as would be easily understood by one of skill in the art.

As explained above, applicants believe that the present specification discloses sufficient guidance necessary for one of skill in the art to easily understand and practice gene therapy as recited in claim 3.

Applicants further note that the examiner alleges that the effect of gene therapy is unpredictable, citing three publications, Anderson WF, *Nature*, Vol. 392 (SUPP), pp. 25-30 (1998), Romano et al., *STEM CELLS*, vol. 18, pp. 19-39 (2000), and Golab, *CYTOKINE*, vol. 12, no. 4, pp. 332-338 (2000), and then denies the usefulness of the present invention as recited in claim 3.

With due respect to the examiner, applicants fully disagree with the examiner's position. In general, gene therapy is attempted only in patients who are in a very severe situation, where the patient has no other choice. It is therefore not surprising that gene therapy gives only a small number of successful cases or indistinct effects on treatment of the diseases. Nevertheless, it should be noted that the usefulness of gene therapy should not be denied so long as there is a case in which gene therapy exhibits its effect. Applicants strongly believe that the claimed invention is useful because it provides a new method for treating tumors. However, in deference to the examiner's question set forth in page 6 line 10 of the Office Action, citing Golab, applicants propose to introduce "IFN-γ and/or killer cell-susceptive" before "tumors" in claims 3 and 17. Support for the amendment is found in the specification as filed at page 10, bottom paragraph.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

The paragraph beginning on page 13, line 6, has been amended as follows:

The reaction mixture was diluted by 100 folds with sterilized distilled water. One μl of the dilution, 5 μl of 10 x Tth PCR reaction solution, 2.2 μl of 25 mM magnesium acetate, 4 μl of 2.5 mM dNTP-mixed solution, one μl of the mixed solution of 2 unit/μl rTth DNA polymerase XL and 2.2 μg/μl Tth Start Antibody in a ratio of 4:1 by volume, 10 pmol of an oligonucleotide with the nucleotide sequence of 5'CTATAGGGCACGCGTGGT-3' (SEQ ID NO:13) as a nested primer, and 10 pmol of an oligonucleotide with the nucleotide sequence of 5'TTCCTCTTCCCGAAGCTGTGTAGACTGC-3' (SEQ ID NO:19) as an anti-sense primer, which was chemically synthesized similarly as above, were mixed and volumed up to 50 μl with sterilized distilled water. After incubating at 94°C for one min, the mixture was subjected to 5 cycles of incubations at 94°C for 25 sec and at 72°C for 4 min, followed by 22 cycles of incubations at 94°C for 25 sec and at 67°C for 4 min to perform PCR for amplifying a DNA fragment of the present genomic DNA. The genomic DNA library and reagents for PCR used above were mainly from "PromoterFinder™ DNA WALKING KITS", commercialized by CLONTECH Laboratories, Inc., California, USA.

The paragraph beginning on page 26, line 16 has been amended as follows:

To the wells with the cells were distributed 0.05 ml aliquots of solutions of the polypeptide in Example 4-1, diluted with RPMI-1640 medium (pH 7.4) containing 10 v/v % bovine fetal serum to give desired concentrations. 0.05 ml aliquots of fresh preparations of the same medium with or without 2.5 μg/ml concanavalin A or 50 units/ml recombinant human interleukin 2 were further added to the wells, before culturing in a 5 v/v % CO_2 incubator at 37°C for 24 hr. After the cultivation, 0.1 ml of the culture supernatant was collected from each well and examined on IFN-γ by usual enzyme immunoassay. In parallel, a systems as a control using the polypeptide in Reference for that in Example 4-1 or using no polypeptide was treated similarly as above. The results were in Table 1. IFN-γ in Table 1 were expressed with international units (IU), calculated based on the IFN-γ standard, Gg23-901-530, obtained from the International Institute of Health, USA.

Claims 3 and 17 have been amended as follows:

3(Once-amended). A method for treating IFN-γ and/or killer cell-susceptive tumors using gene therapy, comprising ~~the steps of~~:

transforming tumor cells obtained from a subject in need thereof with ~~the~~ a composition comprising an isolated DNA molecule that comprises a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:1, where Xaa is isoleucine or threonine, and a carrier capable of introducing the isolated DNA molecule into a mammalian cell, wherein said nucleotide sequence consists of the sequence of a fragment of human genomic DNA ~~according to claim 1~~;

proliferating the transformed tumor cells *ex vivo*; and

transplanting the proliferated transformed tumor cells into the subject ~~in need thereof~~ to treat the tumor cells in the subject.

17(Once-amended). A method for treating IFN-γ and/or killer cell-susceptive tumors using gene therapy, comprising ~~the steps of~~:

transforming tumor cells obtained from a subject in need thereof with an isolated DNA molecule comprising a nucleotide sequence encoding the amino acid sequence ~~shown in~~ of SEQ ID NO:1, where Xaa is isoleucine or threonine, wherein ~~the~~ said nucleotide sequence consists of the sequence of a fragment of human genomic DNA;

proliferating the transformed tumor cells *ex vivo*; and

transplanting the proliferated transformed tumor cells into the subject ~~in need thereof~~ to treat the tumor cells in the subject.